

Striving Towards the Optimal SFC Conditions

A Separation Scientist's Guide to Purifying at the Right Step

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Drug Development Process – DMTA Cycle



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Our Road to Zero Carbon

Our **ambition zero carbon** strategy is to take climate action now for healthy people and a healthy planet, by becoming carbon negative across our entire value chain by 2030.

Zero carbon emissions from our global operations (sites and fleet) by the end of 2025.



Figure from "The Green ChemisTREE: 20 years after taking root with the 12 principles" Green Chem. 2018, 20, 1929-1961, DOI: <u>10.1039/C8GC00482J</u>

The Environmental Footprint of API Production



■ API production ■ Tabletting & formulation ■ Packaging ■ Distribution ■ Use ■ Disposal

Process Mass Intensity - PMI



Design of Synthetic Route







Design of Synthetic Route







Examples of Chromatography PMI

Cmpnd	Technique	Type of purification	Incoming crude API (kg)	Outgoing pure API (kg)	Solvent consumption (L)	PMI (kg waste/kg API)
А	SFC	Achiral	1.6	1.3	115	110
В	SFC	Chiral	3.4	1.5	90	160
С	SFC	Achiral	0.3	0.25	100	95
D	SFC	Achiral	1.0	0.9	40	35
E	LC	Chiral	0.8	0.4	1000	1600
F	LC	Achiral	1.0	0.8	825	825
G	SFC	Chiral	0.8	0.55	100	150

The R's of Sustainability





The R's of Sustainability





Example Compound – Synthetic Route





Chiral Screen Set-up



Modifiers							
A: IPA/NH3 20 ml	M C: Me	C: MeOH/NH3 20 mM					
B: EtOH/NH3 20 r	mM D: AC	D: ACN/NH3 20 mM					
Oven 1	Oven 2	Oven 3					
Chiralpak IA	Lux i-A3	Lux A1					
Chiralpak IB-N	Chiralpak IH	Chiralpak IN					
Chiralpak IC	Chiralpak IJ	Lux C1					
Chiralpak ID	Chiralpak IK	Lux C2					
Chiralpak IE	Chiralpak IM	Lux C3					
Chiralpak IF	(S,S) Whelk-O1	Lux C4					

Analytical Separation of 4 Isomers



Example compound – synthetic route





Chiral Screen Set-up



Options from Chiral Screen















50-gram Purification of API Atropisomers



Example compound – synthetic route





Options from Chiral Screen











Continuous Recycling while Purifying



Racemization







Continuous Recycling while Purifying







1.34 kg Purification of Precursor Atropisomers



Comparison between API and Precursor Methods

API method

- Throughput: 10 g/h
- Solvent consumption: 6.4 L/h
 - Theoretical total: 832 L
 - After recycling: 183 L of MeOH (-78%)



Precursor method

- Throughput: 19.5 g/h
- Solvent consumption: 6.7 L/h
 - o Theoretical total: 465 L
 - After recycling: 100 L of EtOH (-78%)



Recap





Thank you.

